

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: H. William Bosch et al.
Title: NOVEL NIMESULIDE COMPOSITIONS
Appl. No.: 10/697,703
Filing Date: 10/31/2003
Examiner: Tristan J. MAHYERA
Art Unit: 1615
Confirmation Number: 8369

DECLARATION UNDER 37 CFR 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, H. William Bosch, hereby declare and state that:

1. I am a citizen of the United States, residing at 237 Rodney Circle, Bryn Mawr, PA 19010.
2. At the time of events detailed in paragraph 4, *infra*, I was an employee of Elan Drug Delivery, Inc., with offices at 3500 Horizon Drive, King of Prussia, PA 19406.
3. I am a co-inventor of the invention disclosed and claimed in the above-referenced application.

4. Prior to June 27, 2003, I instructed my associates, as part of my supervisory role, to prepare nimesulide compositions comprising particles of nimesulide or a salt thereof having an effective average particle size of less than 2000 nm and at least one surface stabilizer adsorbed on the surface of the particles. My work relating to preparing the nimesulide compositions, which occurred prior to June 27, 2003, is documented in the attached exhibits.

5. As shown in Exhibit A (Notebook No. 5822, pages 006-008), the formulation comprising 5% nimesulide and 1% Plasdane[®] S-630 provides a stable nanoparticulate nimesulide composition.

6. As shown in Exhibit B (Notebook No. 5822, pages 009-011), the formulation comprising 5% nimesulide and 1% Plasdane[®] S-630 provides a stable nanoparticulate nimesulide composition.

7. As shown in Exhibit C (Notebook No. 5822, pages 012-014), the formulation comprising 5% nimesulide, 1% Plasdane[®] S-630 and 0.2% DOSS provides a stable nanoparticulate nimesulide composition.

8. As shown in Exhibit D (Notebook No. 5822, pages 015-017), the formulation comprising 5% nimesulide, 1% Plasdane[®] S-630 and 0.05% sodium lauryl sulfate (SLS) provides a stable nanoparticulate nimesulide composition.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

June 27, 2008
Date

H. William Bosch
H. William Bosch

Title Nimesulide (5% API ; 1% S-630)(cont. from pg. 005)**Batch Record for Dispersion Technology Milling Procedures****I. General Information**

| | |
|-------------------|---------------------------------|
| Name | <u>Christian Werty</u> |
| Date | |
| Formula | <u>5% - Nimesulide 1% S-630</u> |
| Continued on Page | <u>007</u> |

II. Quantities Dispensed

| | Quantity | Type | Source | Lot Number |
|----------------|-------------|---------------------|-------------------|------------|
| Media | <u>80 L</u> | <u>Polymill 200</u> | <u>Dow / PMES</u> | |
| Drug Substance | <u>4.25</u> | <u>Nimesulide</u> | <u>Sigma</u> | |
| Stabilizer | <u>0.85</u> | <u>S-630</u> | | |
| Water | <u>77.9</u> | <u>PI</u> | | |
| Other | | | | |

III. Process Parameters

| | |
|----------------|------------------------------------------------------|
| Milling Method | <u>Dynamill (150 cc batch chamber) F915 @ Rm 205</u> |
| Mill Speed | <u>4,200 rpm</u> |
| Temperature | <u>~10 °C</u> |

IV. Notes

| | |
|---------------------------------|-----------------------------------------------------|
| Milling Time: | <u>9:53 - Start milling ; 10:39 - first sample</u> |
| | <u>10:53 - second sample ; 11:41 - third sample</u> |
| | <u>1:10 - Harvest</u> |
| Quantity retained post-milling: | <u>forgot to filter out media before weighing</u> |

* Did not filter out media initially and discarded ~ 1/2 suspension.
Later filtration left ~20 mL of media free suspension.

(cont. on pg. 007)**CONFIDENTIAL**Signature Christian F. Werty

Date

Reviewed and understood by Nico Ryz

Date



Date _____



Title Nimesulide (5 % API, 2 % S-630)

(cont. from pg. _____)

- mix S-630 slowly into DI H₂O w/ mild stirring until dissolved
- add polymill 200 w/ gentle manual stirring
- add API w/ gentle stirring until thoroughly mixed

Batch Record for Dispersion Technology Milling Procedures

I. General Information

| | |
|-------------------|---------------------------|
| Name | Christian West |
| Date | |
| Formula | 5 % Nimesulide, 2 % S-630 |
| Continued on Page | 010 |

II. Quantities Dispensed

| | Quantity | Type | Source | Lot Number |
|----------------|----------|--------------|-----------|------------|
| Media | 80.6 | Polymill 200 | DOW | MM001012 |
| Drug Substance | 7.25 | Nimesulide | Sigma | 117H1019 |
| Stabilizer | 1.70 | S-630 | ISP Tech. | ML90012974 |
| Water | 79.05 | DI | | |
| Other | | | | |

III. Process Parameters

| | |
|----------------|-----------------------------------------------|
| Milling Method | Dynomill (150 cc batch chamber) F915 @ Rm 205 |
| Mill Speed | 4200 rpm |
| Temperature | ~ 10 °C |

IV. Notes

| | |
|---------------------------------|------------------------------------------------|
| Milling Time: | 8:15 Start batch ; 9:15 1 st Sample |
| | 10:15 2 nd Sample ; 11:15 Harvest |
| Quantity retained post-milling: | 49.6 g (58 %) |

(cont. on pg. 010)

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Signature

Christian L. West

Date

Reviewed and understood by

Dr. William Bosch

Date

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Title Nimesulide 5% API, 1% S-630, 0.2% DOSS

(cont. from pg. _____)

Batch Record for Dispersion Technology Milling Procedures**I. General Information**

| | |
|-------------------|-----------------------------|
| Name | Christian F. Wertz |
| Date | |
| Formula | 5% API, 1% S-630, 0.2% DOSS |
| Continued on Page | 013 |

II. Quantities Dispensed

| | Quantity | Type | Source | Lot Number |
|----------------|----------|--------------|-----------|-------------|
| Media | 80.6 | Polymill 200 | DOW | MM001012 |
| Drug Substance | 4.25 | Nimesulide | Sigma | 117H1019 |
| Stabilizer | 0.85 | S-630 | ISP Tech. | MY900012974 |
| Water | 79.73 | PI | | |
| Other | 0.17 | DOSS | Cytec | SD0041815 |

III. Process Parameters

| | |
|----------------|-------------------------------------------------|
| Milling Method | Dynomill (150 cc batch chamber) F915 @ room 205 |
| Mill Speed | 4200 rpm |
| Temperature | 10 C |

IV. Notes

| |
|--------------------------------------------------|
| Milling Time: 8:20 Start batch ; 9:20 1st Sample |
| 11:20 Harvest |
| |
| Quantity retained post-milling: 26.12 g (30.7 %) |

- Solution was significantly less viscous w/ DOSS than previous runs
- Dissolved S-630, then dissolved DOSS w/ gentle stirring (~15 min)
- Slight leak when mill was started - some solution lost

CONFIDENTIAL(cont. on pg. 013)

Signature

Christian F. Wertz

Date

Reviewed and understood by

William Bosch

Date

Title Nimesulide 5% API, 1% S-630, 0.2% DSS

(cont. from pg. 012)

Batch Record for Dispersion Technology Milling Procedures

| | |
|---------------------|-----------------------------|
| Name | Christian F. Wertz |
| Date | |
| Formula | 5% API, 1% S-630, 0.2% DOSS |
| Continued from page | 012 |

IV. Particle Size Data

| | |
|-----------------------------|-------------------------------------------------------|
| Particle Size Analyzer Used | HORIBA LA-910 (s#: 8514870103D) |
| Standards Measured | Lot #: 22569; mean = 205 ; Duke Sci.; 200 nm standard |

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Signature

Date _____

Reviewed and understood by

Date _____

Title Nimesinide 5% API, 1% S-630, 0.2% DOSS(cont. from pg. 013)**Particle Size Stability for Dispersion Technology Formulations****I. General Information**

| | |
|--------------------|-----------------------------|
| Name | Christian F. Wertz |
| Date | |
| Formulation | 5% API, 1% S-630, 0.2% DOSS |
| Notebook reference | |
| Continued on page | |

II. Particle Size Data

| | |
|-----------------------------|-------------------------------------------------------|
| Particle Size Analyzer Used | HORIBA LA-910 (s#: 8514870103D) |
| Standards Measured | Lot #: 22569; mean = 203 ; Duke Sci.; 200 nm standard |

| Elapsed Time | Storage Conditions | Mean, nm | D50, nm | D90, nm | Comments |
|--------------|--------------------|----------|---------|---------|-----------------|
| 1 day | 5°C | 136 | 116 | 223 | no sonication |
| | 5°C | 137 | 116 | 224 | 60 s sonication |
| 2 day | 5°C | 143 | 121 | 238 | no sonication |
| | 5°C | 144 | 122 | 241 | 60 s sonication |
| 5 day | 5°C | 149 | 133 | 239 | no sonication |
| | 5°C | 151 | 135 | 242 | 60 s sonication |
| 7 day | 5°C | 160 | 143 | 259 | no sonication |
| | 5°C | 163 | 146 | 261 | 60 s sonication |
| 21 day | 5°C | 162 | 150 | 252 | no sonication |
| | 5°C | 166 | 155 | 255 | 60 s sonication |
| 35 day | 5°C | 180 | 172 | 276 | no sonication |
| | 5°C | 189 | 180 | 280 | 60 s sonication |
| | | | | | |
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Signature

Christian F. Wertz

Date

Reviewed and understood by

R. William Bosch

Date



Title Nimesulide 5% API, 1% S-630, 0.05% SLS

(cont. from pg. _____)

- Dissolved S-630 in H₂O followed by SLS under gentle mixing
- SLS dissolved very rapidly w/ very little foam

Batch Record for Dispersion Technology Milling Procedures

I. General Information

| | |
|-------------------|-----------------------------|
| Name | Christian F. Wertz |
| Date | |
| Formula | 5% API, 1% S-630, 0.05% SLS |
| Continued on Page | |

4. Quantities Dispensed

| | Quantity | Type | Source | Lot Number |
|----------------|----------|------------------|----------------|-------------|
| Media | 80.6 | Polymill 200 | DOW | MM001012 |
| Drug Substance | 4.25 | Nimesulide | Sigma | 117H1019 |
| Stabilizer | 0.85 | S-630 | ISP Technology | ML900012974 |
| Water | 79.86 | H ₂ O | DI | |
| Other | 0.04 | SLS | | |

III. Process Parameters

| | |
|----------------|-------------------------------------------------|
| Milling Method | Dynomill (150 cc batch chamber) F915 @ room 205 |
| Mill Speed | 4200 rpm |
| Temperature | 10 C |

IV. Notes

| | |
|---------------------------------|------------------------------------------------|
| Milling Time: | 8:22 Start batch ; 9:22 1 st sample |
| | 10:22 Harvest |
| | |
| Quantity retained post-milling: | 67.4 g (80.7 wt %) |

- mill began leaking after first sample was taken from mill

(cont. on pg. 016)

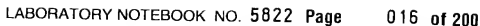
CONFIDENTIAL

Signature Christian F. Wertz

Date _____

Reviewed and understood by W. William Bosch

Date _____



(cont. from pg. 015)

| | |
|---------------------|-----------------------------|
| Name | Christian F. Wertz |
| Date | |
| Formula | 5% API, 1% S-630, 0.05% SLS |
| Continued from page | |

| | |
|-----------------------------|-------------------------------------------------------|
| Particle Size Analyzer Used | HORIBA LA-910 (s#: 8514870103D) |
| Standards Measured | Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard |

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Signature

Clinton J. White

Date _____

Reviewed and understood by

H. Wilhelm Bosch

Date _____

